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MS APPEAL BRIEF - PATENTS
PATENT
4249-0103P

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of		Before the Board of Appeals	
Ching M. CHUNG et al.		Appeal No.:	
Appl. No.:	09/788,476	Group:	1642
Filed:	February 21, 2001	Examiner:	MISOOK YU
Conf.:	6205		
For:	NOVEL GENES AND EXPRESSION PRODUCTS THEREFROM		

APPEAL BRIEF TRANSMITTAL FORM

MS APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

December 10, 2003

Sir:

Transmitted herewith is an Appeal Brief (in triplicate) on behalf of the Appellants in connection with the above-identified application.

☐ The enclosed document is being transmitted via the Certificate of Mailing provisions of 37 C.F.R. § 1.8.

A Notice of Appeal was filed on May 13, 2003, and an Appeal Brief was filed on September 12, 2003.

☒ Applicant claims small entity status in accordance with 37 C.F.R. § 1.27

The fee has been calculated as shown below:

☐ Extension of time fee pursuant to 37 C.F.R. §§ 1.17 and 1.136(a) - $0.00.

☒ Fee for filing an Appeal Brief - $165.00 (small entity) was paid on September 12, 2003.

☐ Check(s) in the amount of $0.00 is(are) attached.

☐ Please charge Deposit Account No. 02-2448 in the amount of $0.00. A triplicate copy of this sheet is attached.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
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DRN/RG:gmh
4249-0103P

Attachment(s)

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(Rev. 11/04/03)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

4249-0103P

In re application of	Before the Board of Appeals
Ching M. CHUNG et al.	Appeal No.:
Appl. No.: 09/788,476	Group: 1642
Filed: February 21, 2001	Examiner: Misook YU
Conf. No.: 6205	

For: NOVEL GENES AND EXPRESSION PRODUCTS THEREFROM

APPEAL BRIEF

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	Before the Board of Appeals
Ching M. CHUNG et al.	Appeal No.:
Appl. No.: 09/788,476	Group: 1642
Filed: February 21, 2001	Examiner: Misook YU
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4249-0103P

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	Before the Board of Appeals
Ching M. CHUNG et al.	Appeal No.:
Appl. No.: 09/788,476	Group: 1642
Filed: February 21, 2001	Examiner: Misook YU
Conf. No.: 6205	
For: NOVEL GENES AND EXPRESSION PRODUCTS THEREFROM	

BRIEF ON APPEAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

December 10, 2003

Sir:

This is an appeal from the Final Rejection, mailed on December 13, 2002, of claim 1.

1. Real party in interest.

The real party in interest in this appeal is the Assignee, National University of Singapore.

2. Related appeals and interferences.

There are no related appeals or interferences.

3. Status of claims.

Claim 1 is rejected. Claims 2-14 and 18 have been cancelled. Claims 15-17 have been indicated to be allowable.

4. Status of Amendments.

In an Advisory Action mailed on April 11, 2003, the Examiner kindly indicated that the Amendment filed on March 13, 2003 would be entered for purposes of appeal. In an Advisory Action mailed on November 26, 2003, the Examiner kindly indicated that the Amendment filed on September 12, 2003 would be entered for purposes of appeal.

5. Summary of invention.

This invention provides diagnostic capabilities based upon the identification of certain gene expression products present in or produced by tissue in subjects having hepatocellular carcinoma or pancreatic adenocarcinoma. These gene expression products are absent, or are present in substantially reduced amounts, in other tissues of said subjects and/or in tissues of subjects not afflicted with those carcinomas. Specification, paragraph [0022]. The terminology "expression product" in this context refers to mRNA transcribed from a nucleotide sequence of a gene and/or to an amino acid sequence (generally in the form of a peptide, polypeptide, or protein) translated from the mRNA molecule. Specification, paragraph [0024].

More specifically, the protein HCC-1 (SEQ ID NO:2), which has 210 amino acids, is localized to the nucleus region of two liver cell lines by immunofluorescence staining. Bioinformatics predictions show that the first 42 amino acids of the protein have identity matches to heterogeneous nuclear ribonucleoproteins from various vertebrae species including human. The rest of the HCC-1 amino acid sequence has no know homology in vertebrates. Specification, paragraphs [0008], [0009], and [0112]. The cDNA of the HCC-1 protein occurs at markedly increased levels in pancreatic adenocarcinoma and

hepatocellular carcinoma. Specification, paragraph [0010].

A gene designated herein as hcc-1 (SEQ ID NO:1) provides the protein expression product HCC-1. A PCR extended form of hcc-1 for use in a vector is shown in SEQ ID NO:3. Specification, paragraphs [0074] and [0111] – [0113]. The hcc-1 gene is expressed in hepatocellular carcinoma tissue and in tissue from pancreatic adenocarcinoma, but is substantially not expressed in other tissue. The gene and its expression product, HCC-1, therefore provide a convenient marker for those cancer conditions. Additionally, they can be used to facilitate the development of antagonists of hcc-1 expression or HCC-1 activity. Specification, paragraphs [0096] and [0119].

6. Issues.

Claim 1 stands rejected as failing to satisfy the requirements of the first paragraph of 35 U.S.C. §112. For the sake of completeness, Applicants will point out both how the specification provides a satisfactory written description of the invention claimed and how the scope of the claim is fully enabled.

7. Grouping of claims.

Claim 1 is the only claim under consideration in this appeal.

8. Argument.

WRITTEN DESCRIPTION

Claim 1 was rejected under the first paragraph of 35 U.S.C. §112 as being drawn to an invention that is not described in the manner prescribed by the statute. This ground of rejection is respectfully traversed.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species *OR* by disclosure or relevant identifying characteristics, such as structure or other physical and/or chemical properties, *OR* by functional characteristics coupled

with a known or disclosed correlation between function and structure. MPEP 2163, II.A.3.a.ii. See *University of California v. Eli Lilly*, 43 USPQ2d 1398 at 1406. Claim 1 states that the sequences which are claimed in addition to SEQ ID NO:1 and SEQ ID NO:3 must (i) have the defined degree of similarity to those specified sequences, ***AND (ii) be hybridizable to those sequences under high stringency conditions, AND*** (iii) must meet the recited functional criterion.

PTO GUIDELINES. The PTO has provided guidelines for applying the written description requirement to biotechnology applications. In *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609, the Court of Appeals for the Federal Circuit adopted the PTO guideline's standard for determining compliance with the written description requirement. Example 9 in those guidelines deals with hybridization. In guideline Example 9, the claim in question is drawn to a genus of nucleic acids all of which must hybridize with SEQ ID NO:1 therein and must encode a protein with a specific activity. Highly stringent hybridization conditions (6XSSC and 65 degrees Celsius) are disclosed. The application in the guidelines discloses only one species (SEQ ID NO:1 itself) falling within the scope of the claimed genus. The analysis provided by the guidelines is as follows:

> ... a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the highly stringent hybridization conditions set forth in the claim yield structurally similar DNAs. Thus, a representative number of species is disclosed, since highly stringent hybridization conditions in combination with the coding function of DNA and the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention.

Similarly, in the present application, the claim in question is drawn to a genus of nucleic acids all of which must hybridize under stringent conditions with a specified sequence and all of which have a recited useful property (expressing differential amounts of mRNA in a normal vs. diseased state of a subject, which difference is detectable.).

The nucleic acids claimed here are even further described – in addition to the two factors paralleling those in the guidelines – as having at least about 60% similarity to the full length of the specified sequences. The requirement in claim 1 that the isolated nucleic acid "hybridizes to SEQ ID NO:1 or SEQ ID NO:3 under conditions of 0.1 x SSC buffer, 0.1% w/v SDS, at a temperature of at least 65°C" is much more limiting than is the requirement that the nucleic acid have at least about 60% similarity to the full length of SEQ ID NO:1 or SEQ ID NO:3. Accordingly, the 60% similarity recitation is unnecessary to satisfy the statute, and the Examiner is hereby authorized to amend claim 1 to read as follows

> 1. An isolated nucleic acid comprising the nucleotide sequence of SEQ ID NO:1 or SEQ ID NO:3 or a nucleotide sequence that hybridizes to SEQ ID NO:1 or SEQ ID NO:3 under conditions of 0.1 x SSC buffer, 0.1% w/v SDS, at a temperature of at least 65°C, wherein an mRNA corresponding to said nucleic acid is differentially or preferentially expressed in human hepatocellular carcinoma tissue or tissue from pancreatic adenocarcinoma relative to other tissue in said subject and/or in subjects not diagnosed with this condition.

by Examiner's Amendment in connection with passing this application to issue.

EXTENSIVE EXPRESS DISCLOSURE. The present specification provides detailed and extensive disclosure relating to the "similarity" recited in the claim, starting in line 6 on page 22 of the specification and continuing through line 8 on page 26 of the specification. "Where there is non-identity at the nucleotide level, 'similarity' includes differences between sequences which result in different amino acids that are nevertheless related to each other at the structural, functional, biochemical and/or conformational levels." "... sequence comparisons between two (or more) polynucleotides are typically performed by comparing sequences of the two polynucleotides over a 'comparison window' to identify and compare local regions of sequence similarity." "For the purposes of the present invention, 'sequence identity' will be understood to mean the 'match percentage' calculated by the DNASIS computer program (Version 2.5 for windows; available from Hitachi Software

Engineering Co., Ltd., South San Francisco, California, USA) ...." "... the present invention contemplates a method for the construction of a nucleic acid molecule comprising a non-naturally occurring nucleotide sequence, said method comprising constructing in a particular reading frame, a contiguous sequence of codons which encode a sequence of amino acids of a polypeptide where one or more codons are selected to express at a higher level in a particular host cell or *in vitro* expression system relative to the corresponding codons in the naturally occurring nucleotide sequence encoding the same polypeptide, wherein the selected codons are preferably used by a host cell, and wherein the codon for Phe may be selected from the group comprising UUU and UUC, the codon for Ser may be selected from the group comprising UCU, UCC, UCA, UCG, AGU and AGC, the codon for Tyr may be selected from the group comprising UAU and UAC, ... the codon for Glu may be selected from the group comprising GAA and GAG, and the codon for Gly may be selected from the group comprising GGU, GGC, GGA, and GGG." The specification herein makes it abundantly clear that Applicants were in possession of the invention recited in claim 1.

Manifestly, claim 1 herein is in fact drawn to an invention described in the manner prescribed by the first paragraph of 35 U.S.C. §112 .

SCOPE

Claim 1 was rejected under the first paragraph of 35 U.S.C. §112 as being drawn to an invention that is claimed in a manner which exceeds the scope of the enablement. The rejection is respectfully traversed.

The Examiner apparently agrees that those skilled in the art would have no difficulty in determining whether a given nucleotide sequence has at least about 60% similarity to SEQ ID NO:1 or to SEQ ID NO:3 after optimal alignment, and in then determining whether that similar sequence is capable of hybridizing to SEQ ID NO:1 or to SEQ ID NO:3 under high stringency conditions defined as 0.1 x SSC buffer, 0.1% w/v SDS at a temperature of at

least 65°C. The Examiner disagrees, however, that a person skilled in the art could then determine by routine screening whether mRNA corresponding to that sequence is differentially or preferentially expressed in human hepatocellular carcinoma tissue or tissue from pancreatic adenocarcinoma relative to other tissue in said subject and/or in subjects not diagnosed with this condition.

As discussed in the present specification, it is well known that some genes are expressed preferentially or exclusively during particular disease conditions such as cancer or autoimmune conditions. The identification of such genes provides a basis for, for instance, diagnosis and developing protocols for down-regulating expression of the gene. Paragraph [0010] herein teaches that a marked increase in hcc-1 cDNA level is observed in pancreatic adenocarcinoma, and that an increase in hcc-1 cDNA level is also observed in well-differentiated hepatocellular carcinoma. Paragraph [0024] teaches that reference herein to an "expression product" includes reference to mRNA transcribed from a nucleotide sequence of a gene and/or an amino acid sequence. These expression products may be identified directly, or they may be identified indirectly, for instance via a complex (e.g., tRNA-amino acid complex) or via an effect.

The Examiner argues that

> In order to determine which other SEQ ID NO:1 or 3-related nucleic acid sequences are biomarker nucleic acid molecules for pancreatic adenocarcinoma or [hepatocellular] carcinoma, one [skilled in the art] has to identify which other nucleic acid molecules are differentially expressed in those cancer patients ....

Why must one determine which other nucleic acid molecules are differentially expressed? The present invention is looking for a single marker indicative of the specific tumors of interest. For the purposes of the present invention, there is no interest in the complete expression profile of these tumors.

In determining whether an isolated nucleic acid falls within the scope of claim 1, a person skilled in the art would first determine whether the nucleic

acid in question had at least about 60% similarity to SEQ ID NO:1 or to SEQ ID NO:3. Assuming the nucleic acid in question passed that test, the person skilled in the art would then determine whether it hybridizes to SEQ ID NO:1 or or to SEQ ID NO:3 under the stringent test recited in claim 1. If the nucleic acid in question were found to pass this second test too, it would necessarily have a great deal in common structurally with SEQ ID NO:1 or SEQ ID NO:3, and its expression profile would likely parallel those of the reference sequence.

With all of these limitations and sources of guidance built in by claim 1, it is not seen that an unduly large number of clinical and control samples, as argued by the Examiner, would be required to fine tune the analysis of any differences between the relevant expression profile of the candidate nucleic acid and the expression profile of SEQ ID NO:1 or SEQ ID NO:3. Moreover, the specification herein -- see e.g. paragraphs [0114] and [0115] -- provides ample exemplification of how to determine whether a nucleic acid meets the requirements set forth in claim 1.

It is respectfully submitted that the genus defined by the present claims is clearly delimited, fully supported, and does not require undue experimentation, given the explanatory disclosure in the specification and the sophistication of those skilled in the relevant art.

SUMMARY AND CONCLUSION

In the Advisory Action of April 11, 2003, the Examiner found Applicants' arguments unconvincing "because the limitation '60 % identity' along with 'differentially or preferentially expressed' could include many other unrelated genes".

The Examiner appears to have overlooked, however, that claim 1 requires that the sequences which claimed in addition to SEQ ID NO:1 and SEQ ID NO:3 must have the defined degree of similarity to those specified sequences ***and be hybridizable t th se sequences under high stringency conditi ns and*** meet the recited functional criterion.

As noted above, the PTO has provided guidelines for applying the written description requirement to biotechnology applications. Example 9 in those guidelines deals with hybridization. In guideline Example 9, the claim in question is drawn to a genus of nucleic acids all of which must hybridize with SEQ ID NO:1 and must encode a protein with a specific activity. Highly stringent hybridization conditions (6xSSC and 65 degrees Celsius) are disclosed. The application in the guidelines discloses only one species (SEQ ID NO:1 itself) falling within the scope of the claimed genus. The analysis provided by the guidelines is as follows:

> ... a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the highly stringent hybridization conditions set forth in the claim yield structurally similar DNAs. Thus, a representative number of species is disclosed, since highly stringent hybridization conditions in combination with the coding function of DNA and the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention.

Similarly, in the present application, the claim in question is drawn to a genus of nucleic acids all of which must hybridize under stringent conditions with a specified sequence and all of which have a recited useful property (expressing differential amounts of mRNA in a normal vs. diseased state of a subject, which difference is detectable.). The nucleic acids claimed here are even further described as -- in addition to the two factors paralleling those in the guidelines -- having at least about 60% similarity to the full length of the specified sequences.

In determining whether an isolated nucleic acid falls within the scope of claim 1, a person skilled in the art would first determine whether the nucleic acid in question had at least about 60% similarity to SEQ ID NO:1 or to SEQ ID NO:3. Assuming the nucleic acid in question passed that test, the person skilled in the art would then determine ***whether it hybridizes to SEQ ID NO:1 r t SEQ ID NO:3 under th stringent c nditi ns recited*** in claim 1. In fact, the stringency recited in claim 1 (0.1xSSC, 65°C) is even higher than the

conditions in guideline Example 9 (6xSSC, 65°C), due to the lower salt concentration recited in claim 1 herein. If the nucleic acid in question were found to pass this second test too, it would necessarily have a great deal in common structurally with SEQ ID NO:1 or SEQ ID NO:3, and its expression profile would likely parallel those of the reference sequence. The specification herein -- see e.g. paragraphs [0114] and [0115] -- provides ample exemplification of how to determine whether a nucleic acid meets the requirements set forth in claim 1.

Clearly, the rejection of record under the first paragraph of 35 U.S.C. §112 cannot be sustained, and its withdrawal is respectfully solicited. It is also respectfully requested that this application be passed to issue with claims 1 and 15-17.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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9. Appendix

1. An isolated nucleic acid comprising the nucleotide sequence of SEQ ID NO:1 or SEQ ID NO:3 or a nucleotide sequence, having at least about 60% similarity to the full length of SEQ ID NO:1 or SEQ ID NO:3, that hybridizes to SEQ ID NO:1 or SEQ ID NO:3 under conditions of 0.1 x SSC buffer, 0.1% w/v SDS, at a temperature of at least 65°C, wherein an mRNA corresponding to said nucleic acid is differentially or preferentially expressed in human hepatocellular carcinoma tissue or tissue from pancreatic adenocarcinoma relative to other tissue in said subject and/or in subjects not diagnosed with this condition.